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(54) **Title:** USE OF VITAMIN E TOCOPHERYL DERIVATIVES IN OPHTHALMIC COMPOSITIONS

(57) **Abstract**

Disclosed are ophthalmic compositions containing vitamin E tocopheryl derivatives which are comfortable and non-irritating. In addition, these vitamin E tocopheryl derivatives significantly increase the aqueous solubility of certain poorly soluble ophthalmic agents.

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USE OF VITAMIN E TOCOPHERYL DERIVATIVES IN OPHTHALMIC COMPOSITIONS

Background of the Invention

The present invention relates generally to ophthalmic compositions. In particular, the present invention relates to the use of certain vitamin E tocopheryl derivatives to provide comfortable, non-irritating ophthalmic compositions. In addition, the present invention relates to the use of these vitamin E tocopheryl derivatives to increase the solubility of poorly soluble ophthalmic agents in aqueous compositions. For purposes of the present specification, the vitamin E tocopheryl derivatives useful in the present invention shall be referred to as "vitamin E tocopheryl derivatives" or "vitamin E derivatives" or "TPGS."

Stinging and burning sensations, as well as general discomfort, are often associated with the topical ophthalmic application of certain types of ophthalmic agents. It is believed that such ocular discomfort is due to the presence of certain functional groups in these agents. Examples of such agents which produce ocular discomfort include, but are not limited to: -blockers such as betaxolol; prostaglandins and prostaglandin derivatives; muscarinics such as pilocarpine; α-adrenergics such as epinephrine, clonidine and apraclonidine; cholinergics such as carbachol; and non-steroidal anti-inflammatory drugs ("NSAIDs") such as diclofenac and suprofen.

There have been a number of attempts to formulate topical ophthalmic compositions to reduce the inherent discomfort associated with these ophthalmic agents. Such attempts include those described in US 4,559,343 (Han et al.), US 4,911,920 (Jani et al.), US 5,093,126 (Jani et al.), and US 5,212,162 (Missel et al.). Han et al. describe the addition of xanthine derivatives, such as caffeine, to decrease the stinging associated with topical ocular application of NSAIDs. The two Jani et al. references teach the addition of certain ion-exchange resins to

compositions of -blockers to increase comfort and to provide sustained release. Missel et al. teach combinations of gelling polysaccharides and finely-divided drug carrier substrates ("DCS") which provide comfortable and sustained release ophthalmic compositions.

In addition, US 4,960,799 (Nagy), discloses storage stable aqueous ophthalmic compositions containing diclofenac and/or its pharmaceutically acceptable salts. The Nagy compositions include EDTA and a solubilizer such as ethoxylated castor oil.

Summary of the Invention

It has now been unexpectedly discovered that the addition of certain vitamin E tocopheryl derivatives to ophthalmic compositions renders such compositions very comfortable and non-irritating. It has also been discovered that these vitamin E derivatives greatly enhance the aqueous solubility of many compounds which are only sparingly soluble in aqueous compositions.

Detailed Description of the Invention

Vitamin E tocopheryl derivatives are water-soluble, biologically-active vitamin E analogues. These vitamin E derivatives have been used as alternatives to vitamin E, especially where water-solubility is desired. In addition, US Patent No.3,102,078 describes the use of these derivatives to solubilize naturally-occurring water-insoluble vitamins, such as vitamins A, D and E. The use of these vitamin E derivatives to enhance the absorption of vitamin A and cyclosporin have also been reported. See, for example, Sokol, R.J. et al., "Improvement of Cyclosporin Absorption in Children after Liver Transplantation by Means of Water-soluble Vitamin E," The Lancet, **338**:212-215 (1991), and Argao, E.A. et al., "*d*-α-Tocopheryl Polyethylene Glycol-1000 Succinate Enhances the Absorption of Vitamin D in Chronic Cholestatic Liver Disease of Infancy and Childhood," Pediatric

Res., **31**(2):146-150 (1992).

The vitamin E tocopheryl derivatives useful in the compositions of the present invention are highly water-soluble polyoxyalkylene glycol esters of vitamin E tocopheryl esters of a dicarboxylic acid. Representative esters of this type include the polyoxyethylene glycol esters of vitamin E tocopheryl esters of a dicarboxylic acid wherein the polyoxyethylene glycol moiety of the ester (sometimes merely referred to as the polyoxyethylene glycol moiety of the ester) has a molecular weight in the range from about 600 to about 6000, preferably in the range from about 600 to about 1500. Such esters and methods for their preparation are disclosed in US Patent No. 2,680,749 (Cawley et al.). The most preferred ester is the α-tocopheryl polyoxyethylene glycol (1000) succinate, a polyoxyethylene glycol ester of α-tocopheryl succinate wherein the polyoxyethylene glycol moiety of the molecule has an average molecular weight of about 1000.

In general, one or more vitamin E derivatives are used in the compositions of the present invention in an amount less than about 30 percent by weight (wt%). If the vitamin E derivatives are used as solubilizing agents, it is preferred to use an amount between about 0.1 and about 20 wt%, most preferably between about 0.1 and about 5 wt%. When the vitamin E derivatives are used to enhance comfort, it is preferred to use an amount between about 0.1 and about 20 wt%, most preferably between about 0.5 and about 10 wt%.

Suitable ophthalmic agents which may be included in the compositions of the present invention and administered via the method of the present invention include, but are not limited to, the racemic and enantiomeric forms and ophthalmically acceptable salts and esters of following types of compounds:

- glaucoma agents, such as: -blockers (e.g., betaxolol, timolol, and carteolol); α-agonists (e.g., apraclonidine and related 2-substituted amino imidazolines); carbonic anhydrase inhibitors; dopamine agonists and antagonists; miotic

cholinergics (e.g., pilocarpine and carbachol); prostaglandins and prostaglandin derivatives; ACE inhibitors; steroids (e.g., glucocorticoids and angiostatic steroids); and calcium channel blockers;

- anti-hypertensives;
- non-steroidal anti-inflammatory agents, including but not limited to those classified as aryl- or heteroaryl- alkanoic acids such as diclofenac, flurbiprofen, suprofen, ketorolac, indomethacin and ketoprofen;
- steroidal anti-inflammatory agents, such as fluorometholone, dexamethasone, prednisolone, tetrahydrocortisol and triamcinolone;
- anti-bacterials and anti-infectives, such as aminoglycosides (e.g., tobramycin); quinolones (e.g., ciprofloxacin and ofloxacin); beta-lactams (e.g., cephalosporins such as cefamandole);
- anti-fungals, such as natamycin;
- anti-virals, such as acyclovir and ganciclovir;
- anti-cataract agents and anti-oxidants;
- anti-allergics;
- anti-metabolites, such as 5-fluorouracil (5-FU) and methotrexate;
- immunosuppressants, such as cyclosporin, FK-506 and leflunimide;
- growth factors such as EGF, FGF, PDGF; and
- prodrugs of the drug classes listed above.

Combinations of ophthalmic agents may also be used in the compositions of the present invention. Further, in formulations without ophthalmic agents, the present invention may also serve to supplement tears in the prevention or treatment of dry eye.

The compositions of the present invention may additionally include other ophthalmically acceptable components: for example, buffers (e.g., phosphate, borate and citrate), chelating agents (e.g., EDTA), preservatives, (e.g., benzalkonium chloride, Polyquad® and Dymed®) and tonicity agents (e.g., sodium chloride and mannitol). The compositions of the present invention may also include viscosity modifying agents such as: cellulosic ethers, such as, hydroxypropyl methyl cellulose (HPMC), hydroxyethyl cellulose (HEC), ethyl hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, and carboxymethyl cellulose; carbomers (Carbopol); polyvinyl alcohol; polyvinyl pyrrolidone; alginates; carrageenans; and guar, karaya, agarose, locust bean, tragacanth and xanthan gums. The concentration of such viscosity modifiers will vary between about 0.1 to about 5 wt%, but such formulations will generally have a viscosity between about 10 and

about 1000 centipoise.

The ophthalmic compositions containing TPGS may additionally contain polymers which will undergo sol-to-gel transition upon exposure to physical or chemical stimuli, such as changes in pH, ion concentration, and/or temperature.

The ophthalmic agents contained in the compositions of the present invention may optionally be encapsulated in microparticles. These loaded microparticles can be dispersed in aqueous vehicles containing TPGS to improve comfort. In addition, water-soluble or water-insoluble complexes of the ophthalmic agent can be incorporated in a vehicle containing TPGS. Example of water-soluble complexes include traditional complexes formed between the ophthalmic agent and caffeine, cyclodextrins, salicylates, benzoates. Examples of water insoluble complexes include ophthalmic agent - drug resin complexes.

The following examples are presented to illustrate further various aspects of the present invention, but are not intended to limit the scope of the invention in any respect.

EXAMPLE 1

The following formulations are representative of preferred compositions of the present invention.

INGREDIENTS	FORMULATION (wt%)						
	A	B	C	D	E	F	G
Sodium Diclofenac	0.1	0.1	0.1	0.1	0.1	---	0.1
Dexamethasone	---	---	---	---	---	0.1	---
Vitamin E TPGS (1000)	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Tromethamine	0.23	0.23	0.23	1.2	1.2	---	0.23
Boric Acid	1.0	0.1	0.1	1.5	1.5	---	1.0
Mannitol	4.0	---	---	3.0	4.0	---	4.0
Benzalkonium Chloride	0.01	0.01	0.01	0.01	0.01	0.01	---
NaC1	---	0.7	0.7	---	---	---	---
Disodium EDTA	0.1	0.1	0.1	0.1	0.1	---	---
HPMC	---	0.1	0.3	0.1	0.3	---	---
Arginine	---	---	---	0.5	---	---	---
HCl and/or NaOH	pH to 7.4						
Purified Water	q.s. 100%						

Preparation:

Formulation D was prepared as follows, and Formulations A-C and E-G were prepared similarly.

A 10% (w/v) stock solution of vitamin E TPGS was prepared as follows. Approximately 150 g of vitamin E TPGS was melted in a beaker by heating on a hot plate with stirring to ensure homogeneity. About 100 grams (g) of the molten

TPGS was then added into 800 milliliters (mL) of near-boiling double distilled water. This mixture was stirred and allowed to cool to room temperature to ensure complete dissolution. Sufficient water was then added to the above solution to make a liter of stock solution.

Sodium diclofenac (0.3 g) was added to 90 mL of 10% TPGS stock solution. After complete dissolution of the diclofenac, the each of following ingredients were sequentially added to the solution with stirring so that each ingredient was completely dissolved before the next ingredient was added: 1.5 g of arginine, 9.0 g of mannitol, 4.5 g of boric acid, 3.6 g of tromethamine and 0.3 g of edetate sodium. To the above solution was added 6.0 mL of 0.5% solution of benzalkonium chloride, followed by the addition of 15 mL of 2% solution of HPMC. An additional 150 mL of water were added and the pH of the formulation adjusted to 7.4 with HCl and/or NaOH. To the resulting solution, enough water was added to bring the total solution volume to 300 mL. The osmolality of the final solution was about 300mOsm/kg.

EXAMPLE 2

The following formulation is another representative composition of the present invention, wherein a prostaglandin complexed with cyclodextrin is formulated in accordance with the teachings of the present invention.

INGREDIENT	CONCENTRATION (wt%)
Prostaglandin	0.25
Hydroxypropyl-β-cyclodextrin	3.0
Tromethamine	1.2
Boric Acid	1.5
Mannitol	1.0
Benzalkonium Chloride	0.01
Disodium EDTA	0.1
Vitamin E TPGS (1000)	3.0
HCl/NaOH	pH to 74.
Purified Water	q.s. 100%

Preparation:

Appropriate amounts of tromethamine, boric acid, mannitol, BAC and EDTA are added to 90 mL of a 10% stock solution of TPGS. In a separate container, 9 g of hydroxypropyl-β-cyclodextrin was dissolved in 150 mL of water. To this is added 0.75 g of a prostaglandin. The two solutions are then mixed together, the pH adjusted to 7.4, and water added to bring the volume to 300 mL.

EXAMPLE 3

The following formulation is another representative composition of the present invention, wherein a prostaglandin bound to Duolite® (cholestyramine resins, available from Rohm & Haas, Philadelphia, Pennsylvania) is formulated in accordance with the teachings of the present invention.

INGREDIENT	CONCENTRATION (wt%)
Prostaglandin	0.25
Duolite®	0.25
Vitamin E TPGS	3.0
Tromethamine	1.2
Boric Acid	1.5
Mannitol	4.0
Benzalkonium Chloride	0.01
Disodium EDTA	0.1
HCl/NaOH	pH to 7.4
Purified Water	q.s. 100%

Preparation:

A prostaglandin (0.75 g) is dissolved in 200 mL of water. Finely divided Duolite (0.75 g) is added, and the solution allowed to equilibrate for 2 hours, during which time about 95% of the drug becomes bound to the resin. In a separate container, appropriate amounts of tromethamine, boric acid, BAC, edetate sodium and mannitol are added to 90 mL of the 10% TPGS stock solution. The two parts are then mixed and the pH adjusted to 7.4 with HCl and/or NaOH. Enough water is then added to the formulation to bring the final volume to 300 mL.

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is claimed is:

1. An ophthalmic composition comprising:

a therapeutically effective amount of one or more ophthalmic agents selected from the group consisting of: anti-glaucoma agents, anti-hypertensives, non-steroidal anti-inflammatory agents, steroidal anti-inflammatory agents, anti-bacterials, anti-infectives, anti-fungals, anti-virals, anti-cataract agents, anti-oxidants, anti-allergics, anti-metabolites, immunosuppressants, growth factors, and prodrugs thereof;

an amount of a vitamin E tocopheryl derivative effective to reduce significantly the discomfort and irritation associated with topical ophthalmic administration of said ophthalmic agent; and

an ophthalmically acceptable vehicle.

2. The composition of claim 1, wherein the ophthalmic agent is a non-steroidal anti-inflammatory agent.

3. The composition of claim 2, wherein the non-steroidal anti-inflammatory agent comprises an aryl- or heteroaryl- alkanoic acid, or an ophthalmically acceptable salt, ester or amide thereof.

4. The composition of claim 3, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of: diclofenac, flurbiprofen, suprofen, ketorolac, indomethacin, ketoprofen and ophthalmically acceptable salts, esters or amides thereof.

5. The composition of claim 4, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac and its ophthalmically acceptable salts, esters or amides.

6. The composition of claim 4, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of suprofen and its ophthalmically acceptable salts, esters or amides.

7. The composition of claim 1, wherein the vitamin E tocopheryl derivative is selected from one or more vitamin E polyoxyethylene glycol esters of a tocopheryl ester of succinic acid wherein the polyoxyethylene glycol moiety of the ester has a molecular weight in a range between about 600 and about 6000.

8. The composition of claim 7, wherein the polyoxyethylene glycol moiety of the ester has an average molecular weight of about 1000.

9. The composition of claim 1, wherein the concentration of vitamin E tocopheryl derivative is less than about 30 percent by weight.

10. The composition of claim 9, wherein the concentration of vitamin E tocopheryl derivative is between about 0.1 and about 20 percent by weight.

11. The composition of claim 10, wherein the concentration of vitamin E tocopheryl derivative is between about 0.5 and about 10 percent by weight.

12. A method for treating or controlling ocular inflammation, comprising the topical ocular application of the composition of claim 2.

13. The method of claim 12, wherein the non-steroidal anti-inflammatory agent comprises an aryl- or heteroaryl- alkanoic acid, or an ophthalmically acceptable salt, ester or amide thereof.

14. The method of claim 13, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of diclofenac and its ophthalmically acceptable salts, esters or amides.

15. A method for improving comfort and reducing irritation in ophthalmic compositions containing one or more ophthalmic agents which are irritating to the eye, comprising the step of adding to the ophthalmic composition an amount of a vitamin E tocopheryl derivative effective to reduce significantly the discomfort and irritation associated with topical ophthalmic administration of said ophthalmic agent.

16. The method of claim 15, wherein the vitamin E tocopheryl derivative is selected from one or more vitamin E polyoxyethylene glycol esters of a tocopheryl ester of succinic acid wherein the polyoxyethylene glycol moiety of the ester has a molecular weight in a range between about 600 and about 6000.

17. The method of claim 16, wherein the polyoxyethylene glycol moiety of the ester has an average molecular weight of about 1000.

18. The method of claim 15, wherein the concentration of vitamin E tocopheryl derivative is less than about 30 percent by weight.

19. The method of claim 18, wherein the concentration of vitamin E tocopheryl derivative is between about 0.1 and about 20 percent by weight.

20. The method of claim 19, wherein the concentration of vitamin E tocopheryl derivative is about 10 percent by weight.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/05730

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/557 A61K31/405 A61K31/38 A61K31/355 A61K31/40
A61K9/00 //(A61K31/557,31:355),(A61K31/405,31:355),
(A61K31/40,31:355),(A61K31/38,31:355),(A61K31/355,31:19)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STP PHARMA SCI. (FRANCE), 1993, VOL. 3, NO. 3, PAGE(S) 266-270, Popovici I. et al 'FORMULATION ET ESSAIS IN VIVO DE COLLYRES HUILEUX D'INDOMETACINE'	1-4,12, 13,15, 18,19
Y	see the whole document	1-20

X	DATABASE WPI Week 9333, Derwent Publications Ltd., London, GB; AN 93-262882 & RO,A,105 131 (INST. MEDICINA FARM. IASI) 25 July 1992	1-4,12, 13
Y	see abstract	1-20

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1995	- 6. 10. 95

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 8813, Derwent Publications Ltd., London, GB; AN 88-089177 & JP,A,63 041 421 (SOGO PHARM CO LTD) 22 February 1988	1
Y	see abstract	7-11, 15-20

Y	DATABASE WPI Week 9346, Derwent Publications Ltd., London, GB; AN 93-365145 & JP,A,5 271 076 (TAISHO PHARM CO LTD) 19 October 1993 see abstract	1-20

Y	BIOCHEMICAL PHARMACOLOGY, vol.39, no.10, 1990 pages 1597 - 1601 R. CARINI ET AL. 'Comparative evaluation of the antioxidant activity of alpha-tocopherol, alpha-tocopherol polyethylene glycol 1000 succinate and alpha-tocopherol succinate in isolated hepatocytes and liver microsomal suspensions' see the whole document	1-20

Y	CONGR. INT. TECHNOL. PHARM., 6TH, vol.4, 1992 pages 254 - 262 M.W. ADAMS 'd-Alpha tocopheryl polyethylene glycol 1000 succinate (Eastman vitamin E TPGS) as an emulsifier and bioenhancer for drugs and lipophilic compounds' see the whole document	1-20

Y	US,A,5 013 751 (S.H. GERSON ET AL.) 7 May 1991 see the whole document	4,6

Y	WO,A,93 03720 (J. TREVITHICK) 4 March 1993 see the whole document	1-20

Y	EP,A,0 578 077 (F. HOFFMANN-LA ROCHE AG) 12 January 1994 see the whole document see claim 1	1-20

Y	EP,A,0 380 367 (STAFFORD-MILLER LTD. ET AL.) 1 August 1990 see the whole document	1-20

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/US 95/05730

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE WPI Week 8539, Derwent Publications Ltd., London, GB; AN 85-239345 & JP,A,60 155 111 (HISAMITSU PHARM KK) 15 August 1985 see abstract -----	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

l. ..rnational application No.

PCT/US95/05730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

REMARK: Although claims 12-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims searched incompletely: 1-20

SEE ANNEX!

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

An agent is not sufficiently characterized by its activity (e.g. anti-glaucoma, anti-hypertensive etc.) or as derivative or prodrug etc. of another compound. Expressions like "non-steroidal anti-inflammatory agent (which) comprises an aryl or heteroaryl-alkanoic acid, or an ophthalmically acceptable salt, ester or amide thereof" etc. do not make sufficiently clear, which compounds are meant. The search has therefore been restricted to the compounds explicitly mentioned in the claims and the examples and to the general inventive concept.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern. al Application No
PCT/US 95/05730

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5013751	07-05-91	NONE		
WO-A-9303720	04-03-93	AU-A-	2434992	16-03-93
EP-A-0578077	12-01-94	US-A-	5252604	12-10-93
		AU-B-	4156493	13-01-94
		CA-A-	2098550	11-01-94
		CN-A-	1086709	18-05-94
		JP-A-	6087741	29-03-94
		JP-B-	7051490	05-06-95
		NZ-A-	248069	22-12-94
EP-A-0380367	01-08-90	US-A-	5032384	16-07-91
		AU-B-	622756	16-04-92
		AU-A-	4876190	09-08-90
		CA-A-	2008739	27-07-90
		DE-D-	69004817	13-01-94
		DE-T-	69004817	14-04-94
		ES-T-	2060014	16-11-94
		JP-A-	2270815	05-11-90